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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,004	04/11/2005	Kenneth D Rice	EX03-054C-US	5083

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EXAMINER	
MURRAY, JEFFREY H	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
03/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,004	RICE ET AL.	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67-104,113-120 and 123-154* is/are pending in the application.

4a) Of the above claim(s) *126-136* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-104,113-120 and 123-125, 137-154* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/24/2005, 11/3/2006, 5/7/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to a response to a restriction requirement filed on December 19, 2007. There are seventy-seven claims pending and sixty-six claims under consideration. Claims 105-112, 121, and 122 have been cancelled. Claims 126-136 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 19, 2007. This is the first action on the merits. This invention relates to compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. Even more specifically, the invention relates to quinazolines which inhibit, regulate and/or modulate kinase receptor signal transduction pathways related to the changes in cellular activities as mentioned above, compositions which contain these compounds, and methods of using them to treat kinase-dependent diseases and conditions.

2. Applicant's election with traverse of Group VI in the reply filed on December 19, 2007 is acknowledged. The traversal is on the ground(s) that there should be no restriction requirement. This is not found persuasive. Applicant incorrectly argues using the "independent and distinct" standards when this case is a national stage case and the "unity of invention" standards must be applied. Because there would be a serious search and examination burden if restriction were not required because (a) the inventions have acquired a separate status in the art in view of their different

classification; (b) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries); and, (c) the prior art applicable to one invention would not likely be applicable to another invention.

Examiner has, however, reconsidered the restriction requirement on the extensivity of the current groupings listed. At this point, the examiner has rejoined groups VI-X into one group, where $M^1M^2M^3M^4$ represents a -CH_2-bicycloheterocyclic group. The requirement for restriction is still deemed proper and is therefore made **FINAL**.

Priority

3. Acknowledgment is made of Applicant's claim for domestic priority. This application, U.S. Application No. 10/522,004, filed April 11, 2005, is a national stage application of PCT/US03/21923, filed on July 14, 2003 and claims domestic priority to U.S. Provisional Application No. 60/396,269, filed July 15, 2002 and U.S. Provisional Application No. 60/447,212, filed February 13, 2003.

Specification

4. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Claim Objections

5. Claims 67-104, 113-120, 123, 125, 137, 145, 148, and 151-154 are objected to because of the following informalities:

Claims 67-104, 113-120, 123, 125, 137, 145, 148, and 151-154 are objected to for containing non-elected subject matter within the claims. Appropriate correction is required.

6. Applicant is advised that should claims 144 and 147 be found allowable, claims 145 and 148 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112, 1st paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 67-104,113-120 and 123-125, 137-154 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound, composition, stereoisomer, racemate, enantiomer, diastereomer or a pharmaceutically acceptable salt thereof where R^1 is a methoxy group; R^2 is a halogen, alkyl, haloalkyl, methoxy, aryloxy, or piperazinyl group; Z is a -NH- group; and $M^1M^2M^3M^4$ is a -CH_2- attached to one of the following: 1) a 5-octahydrocyclopenta[c]pyrrole group; 2) a 3-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazine group; 3) a 3-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazine group; 4) a 3-hexahydrofuro[3,2-b]furan group; 5) a 3-octahydro-1H-pyrido[1,2-a]pyrazin-1-one group; 6) a 3-hexahydropyrrolo[1,2-a]pyrazin-1(2H)-one

group; 7) a 3-hexahydrothiazolo[4,3-c][1,4]oxazine group; 8) a 3-octahydro-1H-quinolizine group; and, 9) a 5-methyl-2-azabicyclo[2.2.2]octane group, does not reasonably provide enablement for any other residue groups or bicyclic heterocyclic groups other than those previously mentioned, or any geometric isomers or hydrates thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

9. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics* Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant.* Applicant has provided no guidance, examples, or provided any chemical or biological data and/or testing results of a compound, composition, stereoisomer, racemate, enantiomer, diastereomer or a pharmaceutically acceptable salt other than those described above with the specific residue groups and bicyclic heterocyclic groups mentioned.

2) Unpredictability in the art. . Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) ..... " Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

The scope of "hydrate" is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Hydrates cannot be predicted and there fore are not capable of being claimed if the applicant cannot properly enable a particular hydrate.

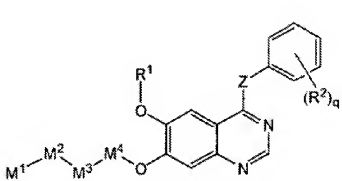
> "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates. (Vippagunta et. al. Advanced Drug Delivery Reviews 48 (2001) 3-26.

3) *Number of working examples.* The compound core depicted with specific substituents represent a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed or preventive agents. Applicant has provided no working examples of any compounds where the R, Z, and $M^1M^2M^3M^4$ moieties are not that previously defined above in the present application.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

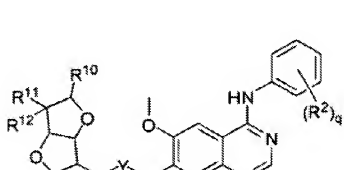
4) *Nature of the invention.* The nature of this invention relates to compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. Even more specifically, the invention relates to quinazolines which inhibit, regulate and/or modulate kinase receptor signal transduction pathways related to the changes in cellular activities as mentioned above, compositions which contain these compounds, and methods of using them to treat kinase-dependent diseases and conditions.

5) Scope of the Claims. The scope of the claims is all of the tens of thousands of compounds represented by general formula I:



I

or Ia:



Ia

where Z is an -NH- group; R_1 is a methyl group; and $M^1M^2M^3M^4$ is a -CH_2- bicyclicheterocyclic group. Thus, the scope of the claims is very broad.

6) *Level of skill in the art.* The artisan using Applicants invention would be a chemist with a Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the

time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for making these compounds or compositions.

Claim Rejections - 35 USC § 112, 2nd paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 2, and 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. The scope of "aryl," heteroaryl," and "heterocyclalkyl," requires clarification since applicants' examples in the specification are not limited to mono- or polyfused carbocycles and heterocycles but appear to include benzo rings fused to heterocyclic rings. See definitions on p.74-76 of the specification. Where applicants define terms with a special meaning, they must set out the special definition with "reasonable clarity, deliberateness and precision". Note *Teleflex v. Ficosa*, 63 USPQ2d 1374; Rexnord Corp v. Laitram Corp. 60 USPQ2d 1851 and MPEP 2111.01.

13. In the absence of the specific moieties intended to effect modification by "substitution" or attachment to the chemical core claimed, the term "substituted" renders the claim in which it appears indefinite in all occurrences wherein applicant fails to articulate by chemical name, structural formula or sufficiently distinct functional

language, the particular moieties applicant regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed.

Conclusion

14. Claims 67-104, 113-120 and 123-125, 137-154 are rejected.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is (571) 272-9023. The examiner can normally be reached on Mon-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a US PTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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